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ELF ATOCHEM NORTH AMERICA, INC.
900 First Avenue, P.O. Box 1536
King of Prussia, PA 19406-0018

Tel: 215-337-6500

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RECD OFFICE OF POLLUTION PREVENTION AND TOXICS
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February 8, 1994

FEDERAL EXPRESS
RETURN RECEIPT REQUESTED

Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M St. S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator

Subject: TSCA Section 8(e) Submission

88940000147

Dear Sir/Madam:

Elf Atochem North America Inc. is submitting the attached study to the Environmental Protection Agency (EPA) pursuant to Toxic Substances Control Act (TSCA) Section 8(e). This study provides information on Dimethyldipropylenetriamine and does not involve effects in humans. The chemical name for this material is 1,3-propanediamine, N'-(3-aminopropyl)-N,N-dimethyl- (CAS No. 10563-29-8). The title of the enclosed study report is Dimethyldipropylenetriamine Skin Sensitization Test in Guinea-Pigs.

Nothing in this letter or the enclosed study report is considered confidential business information of Elf Atochem.

The following is a summary of the adverse effects observed in the skin sensitization test.

Dimethyldipropylenetriamine was tested for potential to produce allergic skin reaction by intradermal injection and skin application to guinea pigs using a modified Magnusson and Klingman method. The test material produced a 32% (6/19) sensitization rate and was classified as a moderate sensitizer.

RECEIVED
3-10-94

36 pgs.

Elf Atochem has not previously filed any 8(e) notices or Premanufacture Notifications (PMNs) on the subject material.

Results from the study report will be incorporated into the current Elf Atochem Material Safety Data Sheet for Dimethyldipropylenetriamine.

Further questions regarding this submission may be directed to me at (215) 337-6892.

Sincerely,

C.H. Farr, PhD, DABT
Manager, Product Safety
and Toxicology

Enclosure

CIT

STUDY TITLE

SKIN SENSITIZATION TEST
IN GUINEA-PIGS
(Maximization method of
Magnusson, B. and Kligman, A.M.)

TEST SUBSTANCE

DIMETHYLDIPROPYLENETRIAMINE
(DMAPAPA)

CENTRE INTERNATIONAL DE TOXICOLOGIE

MISEREY - BP 563 - 27005 ÉVREUX CEDEX - FRANCE / TÉL : (33) 32 29 26 26 / FAX : (33) 32 67 87 05

SPONSOR

Elf Atochem S.A.
La Défense 10
Cédex 42
92091 Paris-la-Défense
France

STUDY TITLE

SKIN SENSITIZATION TEST IN GUINEA-PIGS (Maximization method of Magnusson, B. and Kligman, A.M.)

TEST SUBSTANCE

DIMETHYLDIPROPYLENETRIAMINE (DMAPAPA)

STUDY DIRECTOR

Jack Clouzeau

STUDY COMPLETION DATE

14th January 1994

PERFORMING LABORATORY

Centre International de Toxicologie (C.I.T.)
Miserey - 27005 Evreux - France

LABORATORY STUDY NUMBER

10306 TSG

CONTENTS

STATEMENT OF THE STUDY DIRECTOR

This study was performed in accordance with the protocol agreed upon by Elf Atochem S.A., according to the maximization method of Magnusson and Kligman and according to:
. O.E.C.D. guideline No. 406, 12th May 1981.

The study was conducted in compliance with the principles of Good Laboratory Practice Regulations:
. O.E.C.D. Principles of Good Laboratory Practice, C(81)30(final) Annex 2. May 12, 1981.

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained in the performance of the study.

There were no influences, impacts or circumstances noted which might have impaired the integrity of this study.

This study was performed at the Centre International de Toxicologie (C.I.T.), Miserey, 27005 Evreux, France.

Toxicology

J. Clouzeau
Biologist
Date: 14.1.94

OTHER SCIENTISTS INVOLVED IN THIS STUDY

Pharmacy — J. Richard, Doctor of Pharmacy

Toxicology — C. Pelcot, Study Supervisor

STATEMENT OF THE QUALITY ASSURANCE UNIT

The protocol, study (main) and report were inspected by the C.I.T. Quality Assurance Unit on the following dates:

Inspection	Date of inspection	Date of inspection report
Protocol	17.02.93	17.02.93
Test substance/preparation	14.09.93	14.09.93
Report (first typing)	23.12.93	23.12.93
Report (final)	14.1.94	14.1.94

The other stages (of the same type of studies) were inspected routinely on the following dates:

Animals/housing	8.9.93	8.9.93
Treatment	3.9.93	3.9.93

The inspections were performed in accordance with C.I.T. procedures and the principles of Good Laboratory Practice Regulations.

M. Labiche Date: 14.1.94
Pharmacist
Head of Quality Assurance Unit
and Scientific Archives

SUMMARY

At the request of Elf Atochem S.A., Paris-la-Défense, France, the potential of the test substance, DIMETHYLDIPROPYLENETRIAMINE (DMAPAPA), to induce delayed contact hypersensitivity following intradermal injection and cutaneous application was evaluated in guinea-pigs according to the maximization method of Magnusson and Kligman and O.E.C.D. (No. 406, 12th May 1981). The study was conducted in compliance with the Principles of Good Labo- ratory Practice Regulations.

Methods

Thirty guinea-pigs (15 males and 15 females) were allocated to 2 groups: a control group 1 (5 males and 5 females) and a treated group 2 (10 males and 10 females).
The sensitization potential of the test substance was evaluated after a 10-day induction period during which time the animals were treated with the vehicle (control group) or the test substance (treated group). On day 1, in presence of Freund's complete adjuvant, 0.1 ml of the test substance at a concentration of 1% in the vehicle was administered by intradermal route. On day 8, 0.5 ml of the test substance at a concentration of 25% in the vehicle was applied by cutaneous route during 48 hours by means of an occlusive dressing. After a period of 12 days without treatment, a challenge cutaneous application of 0.5 ml of the vehicle (left flank) and 0.5 ml of the test substance at the Maximum Non-Irritant Concentration of 10% in the vehicle (right flank) were administered to all animals.
The test substance and the vehicle were prepared on a dry compress then were applied to the skin and held in place for 24 hours by means of an occlusive dressing. Cutaneous reactions on the challenge application sites were then evaluated 24 and 48 hours after removal of the dressing.

After the final scoring period, the animals were sacrificed and cutaneous samples were taken from the challenge application sites from all the animals. No histological examination was performed on the cutaneous samples.

The sensitivity of the guinea-pigs in C.I.T. experimental conditions were checked in a recent study with a positive sensitizer: Dinitro 2.4 Chlorobenzene. During induction period the test substance was applied at 0.05% (day 1) and 0.5% (day 8) concentrations. At cutaneous challenge application, 0.1% and 0.5% were tested on both flanks.

Results

During the study, no clinical signs or deaths related to the treatment were observed.

One female of the treated group died on day 9. This was probably due to spontaneous disease which is frequently observed in Guinea-pigs.

The body weight gain of the surviving animals of the treated group was normal when compared to that of the animals of the control group.

After the challenge application of the test substance, no cutaneous reactions were observed in the animals of the control group. In the treated group, cutaneous reactions were noted on the right flank of 12/19 and 11/19 animals after 24 and 48 hours, respectively. The reactions consisted in erythema (very slight, well-defined and moderate to severe).

In addition, a dryness of the skin was noted after 48 hours in 8/19 animals.

No oedema was noted. Inconclusive evidence of sensitization skin reactions (very slight erythema: score of 1) were noted in 6/19 animals after 24 hours. Positive response characterised by a well-defined and moderate erythema (scores of 2 and 3) were noted in 6/19 animals after 24 hours.

The guinea-pigs which were used showed a satisfactory sensitization response in 100% animals using a positive sensitizer (appendix 5).

Conclusion

The test substance DIMETHYLDIPROPYLENETRIAMINE (DMAPAPA) induced positive skin sensitization cutaneous reactions in 6 out of 19, (32%) guinea pigs. The allergenicity level of the test substance was moderate (III) in guinea-pigs.

1. INTRODUCTION

The objective of this study, performed according to maximization method established by Magnusson and Kligman (1), was to evaluate the potential of the test substance, DIMETHYLDIPROPYLENETRIAMINE (DMAPAPA), to induce delayed contact hypersensitivity in guinea-pigs.

The results of the study are of value in predicting the contact sensitization potential of the test material in Man.

During the induction period, the test substance was administered by intradermal route (together with an adjuvant to maximise potential reactions) and cutaneous route. After a rest period of 12 days, a challenge application with the test substance was performed in order to provoke a cutaneous sensitization reaction.

The study was conducted in compliance with:
. O.E.C.D. guideline No. 406, 12th May 1981.

2. MATERIALS AND METHODS

2.1. TEST AND CONTROL SUBSTANCES

2.1.1 Test substance

The test substance, DIMETHYLDIPROPYLENETRIAMINE (DMAPAPA), used in the study was supplied by Elf Atochem S.A.

Documentation supplied by the Sponsor identified the test substance as follows:
. denomination: DIMETHYLDIPROPYLENETRIAMINE (DMAPAPA)
. batch number: P9011
. labelling: DMAPAPA n° d'archivage au CAL: 636/93
. description: colourless liquid
. quantity and container: 100 g in a glass flask
. date of receipt: 26.2.93
. storage conditions: at room temperature and protected from light

Data relating to the characterization of the test substance are documented in a test article description and a certificate of analysis (presented in appendix 1) provided by the Sponsor.

The batch number "P9011", which was absent from the label on the container was confirmed in the protocol.

2.1.2 Vehicle

The vehicle used was sterile isotonic aqueous NaCl solution, batch No. 3019 (Biosédra, 92240 Malakoff, France).

2.1.3 Other substance

The other substance used was Freund's complete adjuvant, batch No. 29829 (Osi, 75739 Paris, France).

2.2. TEST SYSTEM

2.2.1 Animals

Species and strain: Dunkin-Hartley guinea-pigs.
Reason for this choice: species recommended by the international regulations for sensitization studies. The strain used has been shown to produce a satisfactory sensitization response using known positive sensitisers.
Breeder: Centre d'Elevage Lebeau, 78950 Gambais, France.
Number: 30 animals (15 males and 15 females).
Allocation of the animals to the groups: on day -1, the animals were weighed and randomly allocated to 2 groups: a control group 1 consisting of 10 animals (5 males and 5 females) and a treated group 2 consisting of 20 animals (10 males and 10 females).
Weight: on day 1, the animals had a mean body weight of 399 ± 28 g for the males and 391 ± 39 g for the females.
Acclimatization: at least 5 days before the beginning of the study.
Identification of the animals: the animals were identified individually by an ear-tattoo.

2.2.2 Environmental conditions

During the acclimatization period and throughout the study, the conditions in the animal room were as follows:
. temperature: 22 ± 3°C
. relative humidity: 50 ± 20%
. light/dark cycle: 12 h/12 h
The air was non-recycled and filtered.
During the acclimatization period and throughout the study, the animals were housed individually in polycarbonate cages (48 x 27 x 20 cm) equipped with a polypropylene bottle. Sifted and dusted sawdust was provided as litter (SICSA, 92142 Alfortville, France). An analysis of potential residues and major contaminants is performed periodically (Laboratoire Wolff, 92110 Clichy, France).

2.2.3 Food and water

During the study, the animals had free access to "Guinea-pigs sustenance reference 106 diet" (U.A.R., 91360 Villemoisson-sur-Orge, France).
Food was periodically analysed (composition and contaminants) by the supplier.
The diet formula is presented in appendix 2.

Drinking water filtered by a F.G. Millipore membrane (0.22 micron) was contained in bottles.
Bacteriological and chemical analysis of the water and detection of possible contaminants (pesticides, heavy metals and nitrosamines) are performed periodically.
Results are archived at C.I.T.

There were no contaminants in the diet, water or sawdust at levels likely to have influenced the outcome of the study.

2.3. TREATMENT

2.3.1 Preliminary test

A preliminary test was performed to define the concentration to be tested in the main study.

By intradermal route
Determination of the Minimum Irritant Concentration (M.I.C.):
. 24 hours before treatment, the dorsal region of the animals was clipped,
. the test substance was prepared in an appropriate vehicle,
. intradermal administration of the test substance (volume 0.1 ml) at increasing concentrations was performed in order to determine the maximum concentration which does not cause necrosis or ulceration, but a slight irritation,
. evaluation of the potential cutaneous reactions, 24 and 48 hours after injection.

By cutaneous route
Determination of the Minimum Irritant Concentration (M.I.C.) and Maximum Non-Irritant Concentration (M.N.I.C.):
. 24 hours before treatment, the dorsal region of the animals was clipped,
. if necessary the test substance was diluted in an appropriate vehicle,
. 0.5 ml of each concentration was applied to a gauze patch of approximately 4 cm^2 and then held in place by an occlusive dressing for 24 hours (2 concentrations per animal),
. potential cutaneous reactions were evaluated 24 hours after removal of the gauze patches.

2.3.2 Main study

2.3.2.1 Preparation of the animals

For all animals and before each treatment, the application sites were:
. clipped on days -1 and 7 (scapular area 4 x 2 cm),
. clipped again on days 21 and 25 (each flank 2 x 2 cm) and shaved on day 21.

2.3.3 Induction phase by intradermal and cutaneous routes

2.3.3.1 Intradermal route

On day 1, 6 intradermal injections were made into a clipped area (4 x 2 cm) in the scapular region, using a needle (diameter: 0.50 x 16 mm, Terumo: C.M.L., 77140 Nemours, France) mounted on a 1 ml polypropylene syringe (0.01 ml graduations, Record: Carrieri, 75005, Paris, France).
Three injections of 0.1 ml were injected into each side of the animal, as follows:

Control group (figure 1)
. Freund's complete adjuvant diluted to 50% with an injectable isotonic solution (NaCl 0.9%),
. vehicle,
. a mixture of 50/50 (v/v) Freund's complete adjuvant diluted to 50% with a sterile isotonic aqueous NaCl solution and the vehicle.

Treated group (figure 2)
. Freund's complete adjuvant diluted to 50% with a sterile isotonic aqueous NaCl solution,
. test substance at a concentration of 1% in the vehicle,
. a mixture of 50/50 (v/v) Freund's complete adjuvant diluted to 50% with a sterile isotonic aqueous NaCl solution, and, the test substance at a concentration of 1% in the vehicle.

2.3.3.2 Cutaneous route

On day 7, the scapular area was clipped. As the test substance is shown to be irritant after occlusive cutaneous treatment during preliminary test, a local irritation by sodium laurylsulphate was not necessary on day 7.

On day 8, a cutaneous application on the 6 injection areas (4 x 2 cm) of the scapular region was performed.

Control group
. application of 0.5 ml of the vehicle.

Treated group
. application of 0.5 ml of a slight irritant concentration of the test substance at a concentration of 25% in the vehicle.

The vehicle and the test substance were prepared on a dry compress (Semes France, 54183 Heillecourt, France), which was then applied to the scapular region and held in place for 48 hours by means of an adhesive hypoallergic dressing (Laboratoires de Pansements et d'Hygiène, 21300 Chenove, France) and an adhesive anallergic waterproof plaster (Laboratoire des Professions Médicales, 92240 Malakoff, France). No residual test substance was observed at removal of the dressing.
One hour after removal of the occlusive dressing, cutaneous reactions were recorded.

2.3.3.3 Challenge phase

At the end of the rest period on day 22, the test substance was applied at the Maximum Non-Irritant Concentration (M.N.I.C.) i.e. at a concentration of 10% in the vehicle.
On day 22, the animals from both groups received an application of 0.5 ml of the M.N.I.C. of the test substance on the posterior right flank, and 0.5 ml of the vehicle on the posterior left flank. This application was performed using a 1 ml plastic syringe (0.01 ml graduations, Terumo: C.M.L., 77140 Nemours, France). The articles were prepared on a dry compress (Semes France, 54183 Heillecourt, France), then applied to the skin. The compress was held in contact with the skin for 24 hours of means by an occlusive, hypoallergic dressing (Laboratoires de Pansements et d'Hygiène, 21300 Chenove, France) and an adhesive anallergic waterproof plaster (Laboratoire des Professions Médicales, 92240 Malakoff, France).

No residual test substance was observed at removal of the dressing.

2.4. SCORING OF CUTANEOUS REACTIONS

Twenty-four and 48 hours after removal of the dressing from the challenge application site, the both flanks of the treated and control animals were observed in order to evaluate cutaneous reactions, according to the following scale:

Erythema and eschar formation

. No erythema 0
. Very slight erythema (barely perceptible) 1
. Well-defined erythema 2
. Moderate to severe erythema 3
. Severe erythema (beet redness) to slight eschar formation (injuries in depth)..... 4

Oedema formation

. No oedema 0
. Very slight oedema (barely perceptible) 1
. Slight oedema (visible swelling with well-defined edges) 2
. Moderate oedema (visible swelling raised more than 1 millimetre) 3
. Severe oedema (visible swelling raised more than 1 millimetre and extending beyond the area of exposure)..... 4

Any other lesions were noted.

2.5. CLINICAL EXAMINATIONS

The animals were observed twice a day during the study in order to record clinical signs and to check for mortality.

2.6. BODY WEIGHT

The animals were weighed individually on the day of allocation into the groups, on the first day of the study (day 1) and then on days 8, 15 and 25.

2.7. PATHOLOGY

2.7.1 Necropsy

A macrosocopic examination of the main organs was performed on the animal found dead during the study.
On day 25, after the 48-hour observation period, the surviving animals were sacrificed by CO_2 inhalation in excess.

2.7.2 Cutaneous samples

On day 25, a skin sample was taken from the treatment sites of the posterior left and right flanks of all animals. The samples were preserved in 10% buffered formalin.

2.7.3 Microscopic examination

No histological examinations were performed.

2.8. DETERMINATION OF THE ALLERGENICITY LEVEL

The treated animals show a positive reaction if macroscopic cutaneous reactions are clearly visible (erythema and/or oedema ≥ 2) and different from those of the control animals, or, if "doubtful" macroscopic reactions are confirmed at microscopic examination as being due to the sensitization process. Sensitization reactions are characterized at microscopic examination by basal spongiosis, reactional acanthosis of the epidermis and infiltration of mononucleated cells into the dermis (1).

Determination of the allergenicity level
The allergenicity level of the test substance is calculated by comparing the number of animals showing positive reactions with the number of surviving treated animals at the end of the study.

% of animals showing a reaction	Allergenicity level	Classification
0 - 8	I	very weak
9 - 28	II	weak
29 - 64	III	moderate
65 - 80	IV	strong
81 - 100	V	very strong

According to the E.E.C. directive 91/325/E.E.C. published in the Journal Officiel des Communautés Européennes, when the reactions are positive in at least 30% of the treated animals, the test substance has sensitization properties and the sentence "R 43: May cause sensitization by skin contact" must be applied.

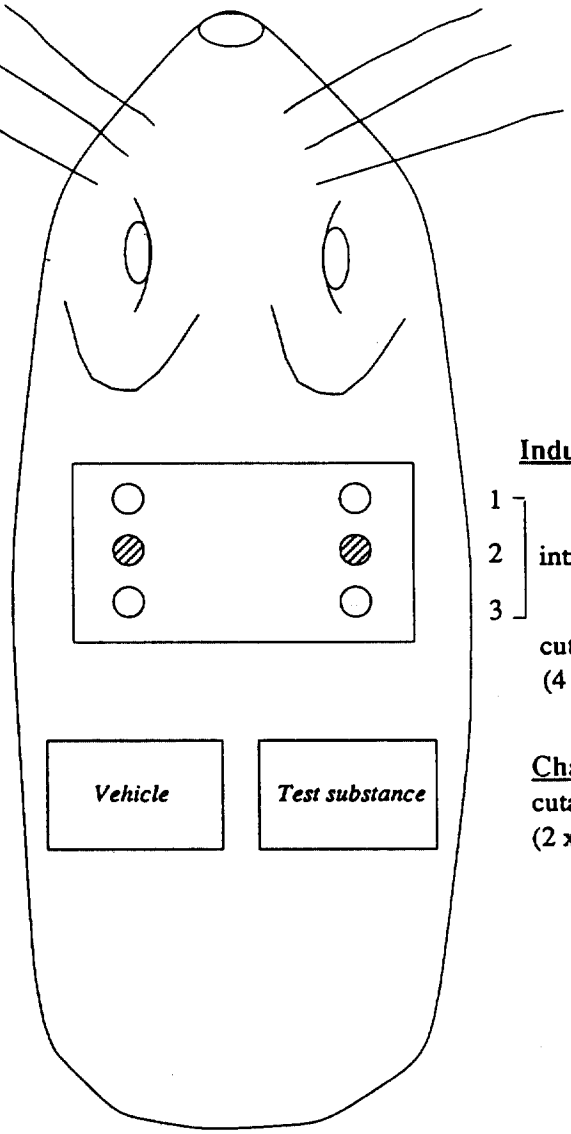
(1) Duprat, P. ; Delsaut. L. ; Gradiski, D. ; Lepage, M. : Investigations histo–pathologiques et cytologiques lors de la mise en évidence, chez le cobaye, d'une allergie cutanée de type retardé. Revue Méd. Vét. 127: 7, 1083-1101 (1976).

2.9. SUMMARY DIAGRAMS

Figure 1: control group

Chronology

Day -1 Clipping of the scapular region
Day 1 Intradermal injection
Day 7 Clipping
Day 8 Application covered by an occlusive dressing
Day 10 Removal of dressing and scoring after one hour
Day 21 Clipping and shaving of the flanks
Day 22 Challenge application covered by an occlusive dressing
Day 23 Removal of dressing
Day 24 First scoring
Day 25 Second scoring, sacrifice of the animals, clipping and skin samples

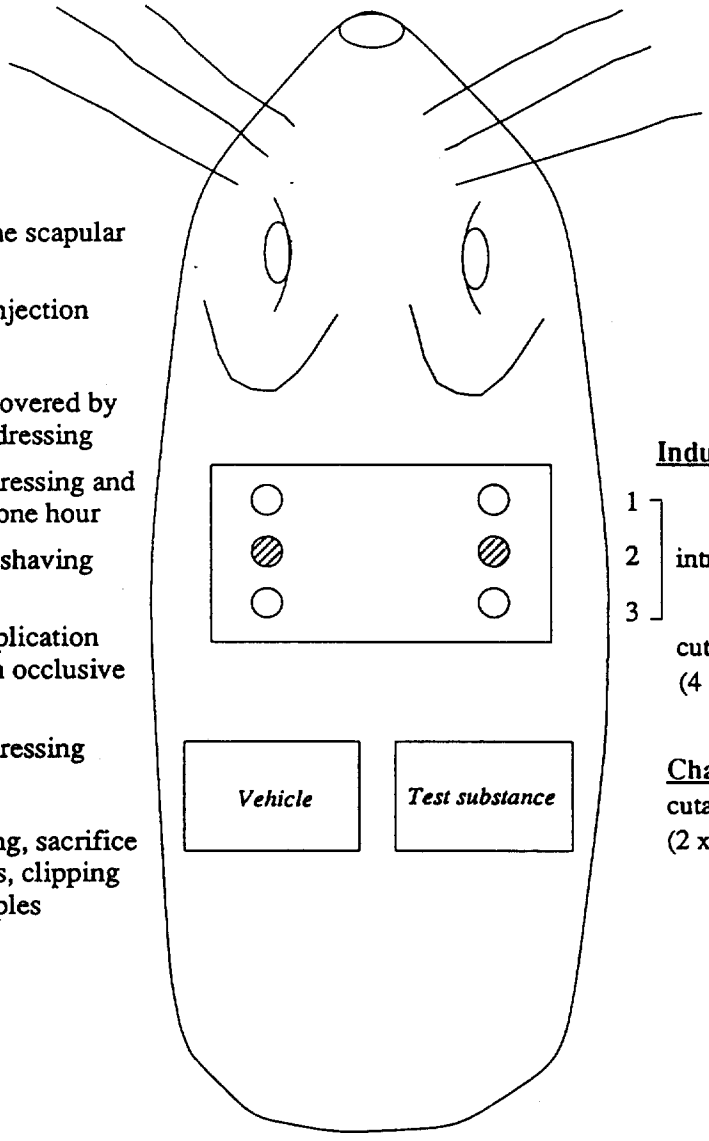


Intradermal injections
1 – 50% Freund's complete adjuvant and NaCl 0.9% solution
2 – vehicle
3 – 1 + 2, 50/50 (v/v)

Figure 2: treated group

Chronology

Day -1	Clipping of the scapular region
Day 1	Intradermal injection
Day 7	Clipping
Day 8	Application covered by an occlusive dressing
Day 10	Removal of dressing and scoring after one hour
Day 21	Clipping and shaving of the flanks
Day 22	Challenge application covered by an occlusive dressing
Day 23	Removal of dressing
Day 24	First scoring
Day 25	Second scoring, sacrifice of the animals, clipping and skin samples



Intradermal injections

○	1	50% Freund's complete adjuvant and NaCl 0.9% solution
▨	2	test substance and vehicle
○	3	1 + 2, 50/50 (v/v)

2.10. CHRONOLOGY OF THE STUDY

The chronology of the study is summarized as follows:

Procedure	Date	Day
Arrival of the animals	9.9.93	- 5
Allocation of the animals into groups	13.9.93	- 1
Weighing, induction by intradermal injection	14.9.93	1
Weighing, induction by cutaneous route	21.9.93	8
Removal of occlusive dressings and scoring of local reactions after 1 hour	23.9.93	10
Weighing	28.9.93	15
Challenge cutaneous application	5.10.93	22
Removal of occlusive dressings	6.10.93	23
Scoring of cutaneous reactions after		
. 24 hours	7.10.93	24
. 48 hours	8.10.93	25
Weighing, sacrifice of the animals and skin samples	8.10.93	25

2.11. ARCHIVES

The study archives:
. protocol and possible amendments,
. raw data,
. correspondence,
. final study report and possible amendments,
. possible histological specimens:
- tissues in preservative
- blocks
- slides

are stored in the premises of C.I.T., Miserey, 27005 Evreux, France, for 5 years after the end of the *in vivo* study. At the end of this period, the study archives will be returned to the Sponsor.

3. RESULTS

3.1. PRELIMINARY STUDY

3.1.1 Administration by intradermal route

The maximal administrable concentration by intradermal route was 75% of the test substance in the vehicle in presence of Freund's complete adjuvant. Several tests were performed to determine the minimal irritant concentration which did not provoke necrosis or ulceration.

Concentration of the test substance %	Scoring after treatment 24 hours	48 hours
1	(1)	(1)
10	(1)	(1)
25	(1)	(1)

Concentration used in the main study is 1% of the test substance.
(1) a black colouration of the treatment site by residual test substance had prevented the evaluation of cutaneous reactions.

3.1.2 Application by cutaneous route

The maximal applicable concentration by cutaneous route was 75% of the test substance in the vehicle. Several tests were performed to determine the M.I.C. and the M.N.I.C. after application of the test substance covered by an occlusive dressing for 24 hours.

Concentration of the test substance %	Scoring 24 hours after removal of the dressing (2)
5	no cutaneous reactions
10	no cutaneous reactions
25	well-defined erythema
50	moderate to severe erythema
75	crust and well-defined erythema
100	crust (superficial necrosis)

M.I.C. is 25% of the test substance.
M.N.I.C. is 10% of the test substance.

(2) No residual was observed.

3.2. MAIN STUDY

3.2.1 Clinical examinations

No clinical signs or mortalities related to the treatment were observed during the study.

Between day 1 and 8, a marked decrease in body weight was noted in one female (No. 46) of the treated group. The female was found dead on day 9. Since only one female of the treated group died and spontaneous disease is frequently the cause of death in Guinea pigs, no treatment related observations were recorded during the study.

The bodyweight gain of the survivings animals of the treated group was normal when compared to that of the control group (figures 3 and 4,appendix 3).

3.2.2 Scoring of cutaneous reactions (appendix 4)

3.2.2.1 End of the induction period

On day 10, after removal of the dressing , irritation in the control group and in the treated group were observed at the intradermal injections sites on the scapular area.

3.2.2.2 Challenge application

After the challenge application, a very slight (1), well-defined (2), moderate to severe (3) erythema was observed at the following frequency:

Erythema

Groups	Sex	Erythema score	Scoring of the cutaneous parameters			
			24 hours		48 hours	
			LF	RF	LF	RF
Control 1	Male	0	5/5	5/5	5/5	5/5
Treated 2	Male	0	10/10	4/10	10/10	5/10
		1	-	3/10	-	3/10
		2	-	3/10	-	2/10
Control 1	Female	0	5/5	5/5	5/5	5/5
Treated 2	Female	0	9/9	3/9	9/9	3/9
		1	-	3/9	-	5/9
		2	-	2/9	-	-
		3	-	1/9	-	1/9

LF: left flank (control)
RF: right flank (treated)

After the challenge application of the test substance, no cutaneous reactions were observed in the animals of the control group. A positive response characterised by a well-defined and a moderate to severe erythema was observed on the right flank of 6/19 treated animals after 24 hours and 3/19 animals after 48 hours. No oedema was noted. The reactions noted in a 6/19 animals after 24 hours and 8/19 animals after 48 hours (very slight erythema) were considered to be due to a slight irritant or a "doubtful" sensitization effect of the test substance. After 48 hours, a dryness of the skin in 8/19 animals of the treated group was noted. As no signs of irritation were noted in the animals of the control group, the cutaneous reactions noted in the 6/19 animals (after 24 hours) were considered to be due to a sensitization effect of the test substance.

3.2.3 Pathology

Macroscopic examination of the main organs of the animal (female No. 46) found dead during the study revealed no abnormalities.

4. CONCLUSION

The test substance DIMETHYLDIPROPYLENETRIAMINE (DMAPAPA) induced positive skin sensitization cutaneous reactions in 6 out of 19, (32%) guinea-pigs. The allergenicity level of the test substance was moderate (III) in guinea-pigs.

Figure 3: Male body weight gain (g)

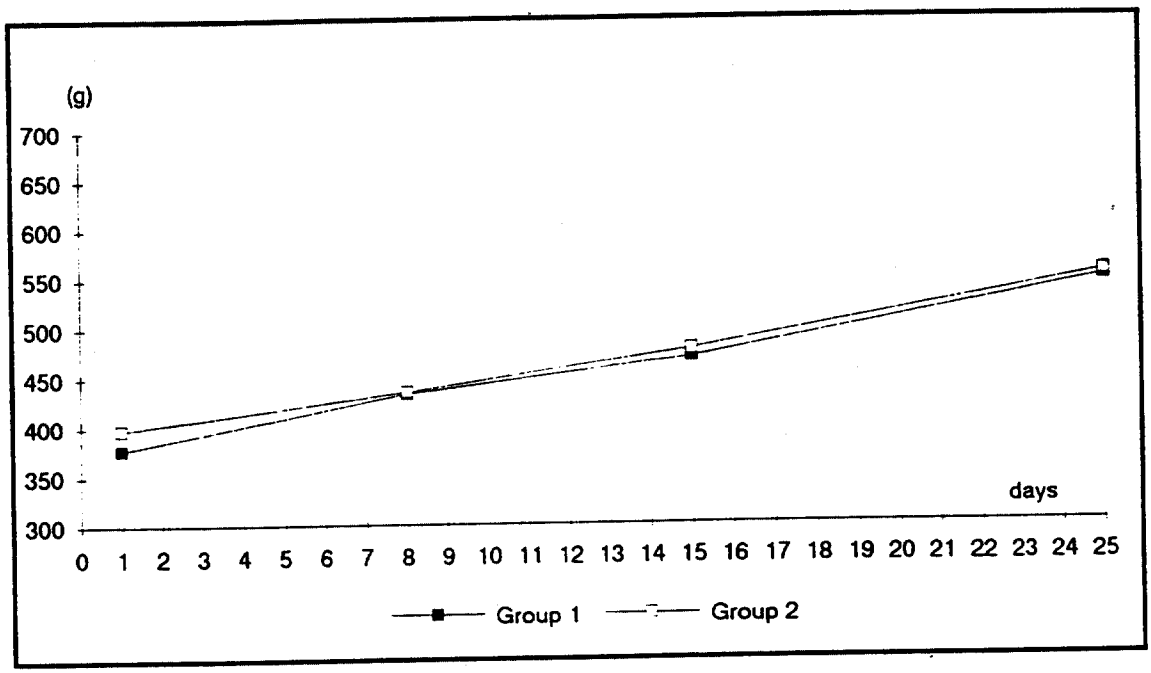
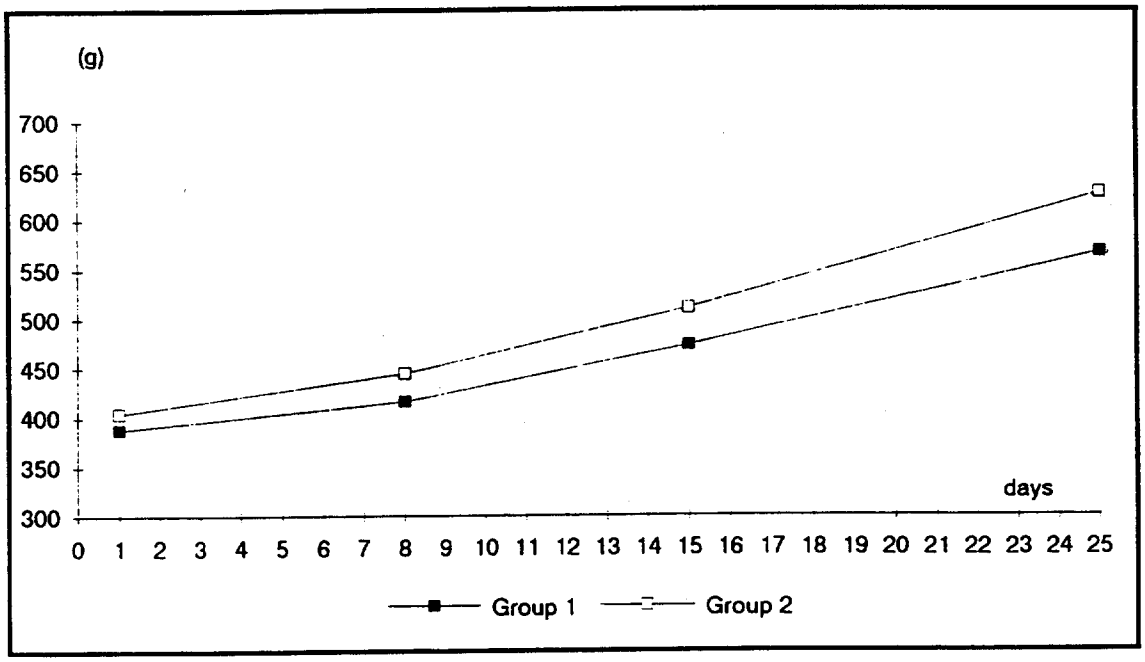


Figure 4: Female body weight gain (g)



APPENDICES

1. Test article description and certificate of analysis

elf atochem

ATO
MAURIENNE

le 01 février 93

A l'attention de M. Bouchy (CAL)
copie M. Régnier

Bulletin d'Analyse
9301 P0355

Produit : DIMETHYLDIPROPYLENETRIAMINE

lot : P90 11.

Pureté	=	99,10 % poids
Impuretés inconnues	:	0,75 % poids
eau	=	0,145 % poids
coloration	:	10-15 Hazen

M. Fournier

QUALITE

TOXICOLOGY DEPARTMENT
CONFIDENTIAL
11 February 1993

elf atochem s.a.
La défense 10, cedex 42
92091 Paris-la-Défense, France

TEST ARTICLE DESCRIPTION

DIMETHYLDIPROPYLENETRIAMINE

STRUCTURAL FORMULA

$(CH_3)_2N\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_3\text{-}NH_2$

IDENTITY

Test article name	:	N,N-Dimethyldipropylenetriamine (DMAPAPA)
Chemical name	:	1,3-propanediamine, N'-(3-aminopropyl)-N,N-dimethyl-
CAS number	:	10563-29-8
EINECS number	:	2341484
Molecular formula	:	159
Molecular weight	:	$C_8H_{21}N_3$
Origin and batch	:	Elf Atochem, La Chambre, P9011
ATOCHEM filing number	:	CAL 636/93
Purity	:	99.1% (w/w)
Analysis number	:	9301P0355

PHYSICAL AND CHEMICAL PROPERTIES

Appearance	:	Clear liquid, ammoniacal odour
Specific gravity	:	0.874 at 20°C
Melting point	:	< -25°C
Boiling point	:	210-230°C at 1013 mbar
Vapor pressure	:	<1.3 mbar at 20°C
Flash point	:	99°C
Solubility	:	freely soluble in water

TOXICOLOGICAL INFORMATIONS AND USE SAFETY

DL_{50} / rat / oral = 1670 mg/kg. Corrosive to the rabbit skin.

STORAGE AND DISPOSAL

Storage	in dark and at room temperature
Expiry date	February 1994
Disposal	incineration

2. Diet formula

Ref: 106
COMPLETE DIET
GUINEA-PIG MAINTENANCE DIET
Appearance: 4.5 mm diameter granules
Conditioning: bags of 25 kgs

Daily portion: water *ad libitum*, Guinea-pigs 35-50 g.

FORMULA %

Cereals	42
Grain biproducts and legumes	46
Vegetable protein (soya bean meal, yeast)	9
Vitamin and mineral mixture	3

AVERAGE ANALYSIS %

Calorific value (KCal/kg)	2600
Moisture	10
Proteins	17
Lipids	3
Carbohydrates (N.F.E.)	49
Fibre	13
Minerals (ash)	8

AMINO ACID VALUES
(calculated in mg/kg)

Arginine	8500
Cystine	2500
Lysine	7200
Methionine	2100
Tryptophan	2000
Glycine	6000

FATTY ACID VALUES
(calculated in mg/kg)

Palmitic acid	3600
Palmitoleic acid	0
Stearic acid	700
Oleic acid	5900
Linoleic acid	11200
Linolenic acid	3000

MINERALS (calculated in mg/kg)

	Nat. input	Input /MC	Total
P	7400	1400	8800
Ca	5400	5600	11000
K	12000	0	12000
Na	1300	1950	3250
Mg	3270	130	3400
Mn	60	40	100
Fe	170	150	320
Cu	10	15	25
Zn	40	45	85
Co	0.1	1.5	1.6
I	0	0	0
Cl	0	0	0

VITAMINS (calculated per kg)

	Nat. input	Synth. input	Total
Vitamin A	3500 IU	7500 IU	11000 IU
Vitamin D3	30 IU	2000 IU	2030 IU
Vitamin B1	6 mg	6.4 mg	12.4 mg
Vitamin B2	5 mg	6.4 mg	11.4 mg
Vitamin B3	22 mg	26 mg	48 mg
Vitamin B6	0.7 mg	2.7 mg	3.4 mg
Vitamin B12	0.003 mg	0.012 mg	0.015 mg
Vitamin C	0 mg	400 mg	400 mg
Vitamin E	15 mg	60 mg	75 mg
Vitamin K3	5 mg	12.6 mg	17.6 mg
Vitamin PP	97 mg	14.5 mg	111.5 mg
Folic acid	2.2 mg	1.3 mg	3.5 mg
P.A.B. acid	0 mg	2.5 mg	2.5 mg
Biotin	0.02 mg	0.06 mg	0.08 mg
Choline	1010 mg	60 mg	1070 mg
Meso-Inositol	0 mg	62.5 mg	62.5 mg

This food is supplemented with stabilized coated vitamin C, avoiding the need of other food substances (greenery, ascorbic acid) if used within 4 months of date of manufacture.

U.A.R., 7 rue Galliéni, Villemoisson, 91360 Epinay-sur-Orge - Tel: 69.04.03.57
Telex: UAR 691716F.

3. Individual body weight values

INDIVIDUAL BODY WEIGHT VALUES
(g)

Groups	Sex	Animals	Days							
			-1	1	(1)	8	(1)	15	(1)	25
1	Male	21	398	413	86	499	26	525	132	657
		22	397	409	-19	390	58	448	61	509
		23	371	399	70	469	40	509	115	624
		24	340	313	67	380	85	465	47	512
		25	400	404	-63	341	77	418	113	531
		M	381	388	28	416	57	473	94	567
		SD	26	42	65	66	25	44	37	69
	Female	36	406	406	61	467	10	477	66	543
		37	405	410	89	499	27	526	101	627
		38	347	332	76	408	53	461	64	525
		39	321	325	2	327	78	405	101	506
		40	410	414	52	466	10	476	66	542
		M	378	377	56	433	36	469	80	549
		SD	41	45	33	68	30	43	20	46
2	Male	26	401	420	18	438	71	509	126	635
		27	380	395	78	473	48	521	137	658
		28	410	422	82	504	61	565	99	664
		29	414	437	-84	353	117	470	152	622
		30	376	404	50	454	49	503	97	600
		31	374	386	31	417	75	492	111	603
		32	393	416	57	473	31	504	107	611
		33	375	375	87	462	55	517	109	626
		34	390	393	1	394	65	459	94	553
		35	405	393	85	478	85	563	124	687
		M	392	404	41	445	66	510	116	626
		SD	15	19	53	45	24	34	19	38
	Female	41	318	340	52	392	46	438	81	519
		42	406	413	69	482	6	488	82	570
		43	440	448	35	483	21	504	58	562
		44	368	387	-11	376	78	454	72	526
		45	431	447	46	493	37	530	66	596
		46	384	388	-47	341				
		47	349	355	40	395	46	441	79	520
		48	414	427	63	490	50	540	62	602
		49	382	387	51	438	-26	412	97	509
		50	362	382	76	458	31	489	85	574
		M	385	397	37	435	32	477	76	553
		SD	38	36	38	55	30	44	12	35

(1) = Body weight gain
M = Mean
SD = Standard Deviation

4. Individual observation of cutaneous reactions

MACROSCOPIC EXAMINATION OF CUTANEOUS REACTIONS

Challenge application

Group	Sex	Animals	Day 24 scoring period (after 24 hours)				Day 25 scoring period (after 48 hours)			
			Erythema		Oedema		Erythema		Oedema	
			LF	RF	LF	RF	LF	RF	LF	RF
Control 1	Male	21	0	0	0	0	0	0	0	0
		22	0	0	0	0	0	0	0	0
		23	0	0	0	0	0	0	0	0
		24	0	0	0	0	0	0	0	0
		25	0	0	0	0	0	0	0	0
	Female	36	0	0	0	0	0	0	0	0
		37	0	0	0	0	0	0	0	0
		38	0	0	0	0	0	0	0	0
		39	0	0	0	0	0	0	0	0
		40	0	0	0	0	0	0	0	0
Treated 2	Male	26	0	2	0	0	0	2/S	0	0
		27	0	1	0	0	0	0	0	0
		28	0	0	0	0	0	0	0	0
		29	0	2	0	0	0	2/S	0	0
		30	0	0	0	0	0	0	0	0
		31	0	2	0	0	0	1/S	0	0
		32	0	0	0	0	0	0	0	0
		33	0	0	0	0	0	0	0	0
		34	0	1	0	0	0	1/S	0	0
		35	0	1	0	0	0	1/S	0	0
	Female	41	0	1	0	0	0	1	0	0
		42	0	0	0	0	0	0	0	0
		43	0	0	0	0	0	0	0	0
		44	0	1	0	0	0	1	0	0
		45	0	0	0	0	0	0	0	0
		46	-	-	-	-	-	-	-	-
		47	0	1	0	0	0	1	0	0
		48	0	2	0	0	0	1/S	0	0
		49	0	2	0	0	0	1/S	0	0
		50	0	3	0	0	0	3/S	0	0

LF: left flank (control)
RF: right flank (treated)
-: dead animal

5. Positive control to check the sensitivity of Dunkin-Hartley guinea-pigs

Purpose: check the sensitivity of Dunkin-Hartley guinea-pigs to a positive control test article

Method	:	Magnusson and Kligman	
Test substance	:	DINITRO 2.4 CHLOROBENZENE	
C.I.T. Study - Date	:	July 1993 (CIT/Study No. 10829 TPG)	
Number of animals	:	5 females	
Induction	:	0.05%	intradermal route day 1
		0.5%	cutaneous route day 8
Challenge application	:	0.1%	right flank
		0.5%	left flank

Conclusion

In our experimental conditions and according to the Magnusson and Kligman method, DINITRO 2.4 CHLOROBENZENE at a concentration of 0.5% induced positive skin sensitization reactions in 100% of the guinea-pigs.

INDIVIDUAL REACTIONS: CHALLENGE PHASE
MACROSCOPIC FINDINGS

Group	Sex	Animals	24-hour scoring period				48-hour scoring period				Conclusion	
			Erythema		Oedema		Erythema		Oedema			
			LF	RF	LF	RF	LF	RF	LF	RF	LF	RF
Treated	Female	16	3	2	0	0	3/S	2/S	0	0	+	+
		17	3	2	0	0	3	1/S	0	0	+	+
		18	4	2	0	0	4	2/S	0	0	+	+
		19	4	2	0	0	4	1/S	0	0	+	+
		20	3	1	0	0	3/S	0	0	0	+	+/-

+ : hypersensitizing reaction
A: scab
S: dryness of the skin
LF: left flank
RF: right flank

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

APR 1 2 1994

C.H. Farr
Manager, Product Safety and Toxicology
Elf Altochem North America, Inc.
900 First Avenue, P.O. Box 1536
King of Prussia, Pennsylvania 19406-0018

This letter formally acknowledges EPA's receipt of information submitted by your organization under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA Section 8(e) Document Control Number (i.e., 8EHQ-0000-0000 Init.) assigned by EPA to your submission(s). Please refer to this cited number when submitting follow-up or supplemental information.

Please note that all submitted correspondence will be placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA Section 8(e) policy statement (43 FR 11110, March 16, 1978).

Confidential submissions submitted pursuant to the TSCA Section 8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims, because substantiation of CBI claims is required at the same time the 8(e) CAP is submitted to EPA. (If not done so already, please ensure that this information is provided to the Agency). When substantiating any/all claims, answer the questions detailed in the following attachment.

For NON-CAP submissions, any confidentiality claims should be supported by submission of information as described in the attachment(s).

12905 A

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ-0294-12905 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Elf Atochem North America, Inc.

SUB. DATE: 02/08/94 OTS DATE: 02/16/94 CSRAD DATE: 03/10/94

CHEMICAL NAME:

CAS#
10563-29-8

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS
(0404) LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

INFORMATION TYPE:		P	F	C
0201	ONCO (HUMAN)	01	02	04
0202	ONCO (ANIMAL)	01	02	04
0203	CELL TRANS (IN VITRO)	01	02	04
0204	MUTA (IN VITRO)	01	02	04
0205	MUTA (IN VIVO)	01	02	04
0206	REPRO/TERATO (HUMAN)	01	02	04
0207	REPRO/TERATO (ANIMAL)	01	02	04
0208	NEURO (HUMAN)	01	02	04
0209	NEURO (ANIMAL)	01	02	04
0210	ACUTE TOX. (HUMAN)	01	02	04
0211	CHR. TOX. (HUMAN)	01	02	04
0212	ACUTE TOX. (ANIMAL)	01	02	04
0213	SUB ACUTE TOX (ANIMAL)	01	02	04
0214	SUB CHRONIC TOX (ANIMAL)	01	02	04
0215	CHRONIC TOX (ANIMAL)	01	02	04

INFORMATION TYPE:		P	F	C
0216	EPI/CI'N	01	02	04
0217	HUM. EXPOS (PROD CONTAM)	01	02	04
0218	HUMAN EXPOS (ACCIDENTAL)	01	02	04
0219	HUMAN EXPOS (MONITORING)	01	02	04
0220	ECO/AQUA TOX	01	02	04
0221	ENV. OCCC/REL/FATE	01	02	04
0222	EMER INCI OF ENV CONTAM	01	02	04
0223	RESPONSE REQEST DELAY	01	02	04
0224	PROD/COMP/CHEM ID	01	02	04
0225	REPORTING RATIONALE	01	02	04
0226	CONFIDENTIAL	01	02	04
0227	ALLERG (HUMAN)	01	02	04
(0228)	ALLERG (ANIMAL)	01	(02)	04
0239	METAB/PHARMACO (ANIMAL)	01	02	04
0240	METAB/PHARMACO (HUMAN)	01	02	04

INFORMATION TYPE:	
0241	IMMUNO (ANIMAL)
0242	IMMUNO (HUMAN)
(0243)	CHEM/PHYS PROP
0244	CLASTO (IN VITRO)
0245	CLASTO (ANIMAL)
0246	CLASTO (HUMAN)
0247	DNA DAM/REPAIR
0248	PROD/USE/PROC
0251	MSDS
0299	OTHER

TRIAGE DATA: NON-CBI INVENTORY
(YES)
NO
DETERMINE

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER:

SPECIES
GP

TOXICOLOGICAL CONCERN:
LOW
(MED) DERMAL SENSITIZATION
HIGH

USE:

PRODUCTION

COMMENTS: Non-CAP

8(E): 12905
MEDIUM - DERMAL SENSITIZATION

Dermal sensitization study in guinea pigs resulted in very slight, well-defined and moderate to severe erythema in 6/19, 5/19 and 1/19, respectively at 1st challenge. At 2nd challenge, 11/19 animals exhibited positive reactions.